FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
216897US0PCT	
U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	
09/926813	
INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE
PCT/JP00/03935	JUNE 16, 2000
PRIORITY DATE CLAIMED	
JUNE 21, 1999	

TITLE OF INVENTION
REMEDIES FOR SKIN ULCER

APPLICANT(S) FOR DO/EO/US
Masahide HIGAKI, et al.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (24) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☒ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☐ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

    PCT/IB/304
    PCT/IB/308
    Form PTO 1449

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/926813	PCT/JP00/03935	216897US0PCT

24. The following fees are submitted:

	CALCULATIONS PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :	
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $1040.00	
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $890.00	
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO $740.00	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) $710.00	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) $100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$890.00
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	$0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	12 - 20 =	0	x $18.00	$0.00
Independent claims	4 - 3 =	1	x $84.00	$84.00
Multiple Dependent Claims **(check if applicable)**.			☐	$0.00
TOTAL OF ABOVE CALCULATIONS =				$974.00
☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				$0.00
SUBTOTAL =				$974.00
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +				$0.00
TOTAL NATIONAL FEE =				$974.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				$0.00
TOTAL FEES ENCLOSED =				$974.00
Amount to be: refunded				$
charged				$

a. ☒ A check in the amount of **$974.00** to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. _____ in the amount of _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **15-0030** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

22850

Surinder Sachar
Registration No. 34,423

Surinder Sachar
SIGNATURE

Norman F. Oblon
NAME

24,618
REGISTRATION NUMBER

Dec. 21 2001
DATE

216897US-0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF :

HIGAKI MASAHIDE ET AL : ATTN: APPLICATION DIVISION

SERIAL NO: NEW U.S. PCT APPLN :
Based on PCT/JP00/03935

FILED: HEREWITH :

FOR: REMEDIES FOR SKIN ULCER

PRELIMINARY AMENDMENT

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231

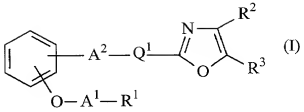
SIR:

Prior to examination on the merits, please amend the above-identified application as follows:

IN THE CLAIMS

Please amend the claims as shown in the marked-up copy following this amendment to read as follows:

3. (Amended) A pharmaceutical composition as claimed in Claim 1, wherein the nonprostanoid prostaglandin I_2 agonist is a compound of the following general formula (I) or a pharmaceutically acceptable salt thereof:



(I)

[wherein R^1 is carboxy or protected carboxy,

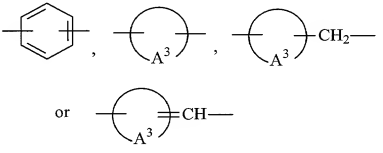
R^2 is aryl which may optionally have one or more suitable substituents,

R^3 is aryl which may optionally have one or more suitable substituents,

A^1 is lower alkylene,

A^2 is a single bond or lower alkylene and

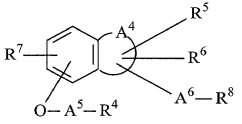
$-Q^1-$ is



(in which

represents cyclo(lower)alkane or cyclo(lower)alkene, which respectively may optionally have one or more suitable substituents)].

4. (Amended) A pharmaceutical composition as claimed in Claim 1, wherein the nonprostanoid prostaglandin I_2 agonist is a compound of the following general formula (II) or a pharmaceutically acceptable salt thereof:



(II)

[wherein R^4 is carboxy or protected carboxy,

R^5 is hydrogen, hydroxy or protected hydroxy,

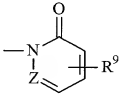
R^6 is hydrogen, hydroxy, protected hydroxy, lower alkyl or halogen,

R^7 is hydrogen or halogen,

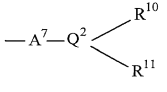
A^5 is lower alkylene,

A^6 is a single bond or lower alkylene and

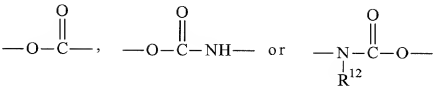
$-R^8$ is



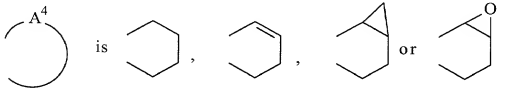
(in which R^9 is mono(or di or tri)aryl(lower)alkyl and Z is N or CH) or



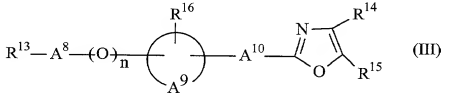
(in which $-A^7-$ is



(in which R^{12} is hydrogen or lower alkyl), Q^2 is N or CH, R^{10} is aryl and R^{11} is aryl), and



5. (Amended) A pharmaceutical composition as claimed in Claim 1, wherein the nonprostanoid prostaglandin I_2 agonist is a compound of the following general formula (III) or a pharmaceutically acceptable salt thereof



(III)

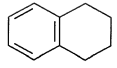
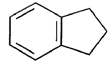
[wherein R^{13} is carboxy or protected carboxy,

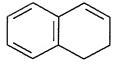
R^{14} is aryl which may optionally have one or more suitable substituents,

R^{15} is aryl which may optionally have one or more suitable substituents,

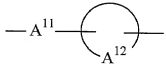
R^{16} is hydrogen, lower alkyl, hydroxy or aryl,

A^8 is lower alkylene,

is  ,  , 

or  ,

$-A^{10}-$ is



(in which $-A^{11}-$ is a single bond, $-CH_2-$ or -CO-,

represents cyclo(C5-C8)alkene, cyclo(C7-C8)alkane, bicycloheptane, bicycloheptene, tetrahydrofuran, tetrahydrothiophene, azetidine, pyrrolidine or piperidine, which respectively may optionally have one or more suitable substituents) or $-X-A^{13}-$ (in which –X– is –O–, –S–, or $–N(R^{17})-$ (R^{17} being hydrogen, lower alkyl or acyl) and A^{13} is lower alkylene which may optionally have one or more suitable substituents) and n is 0 or 1].

6. (Amended) A pharmaceutical composition as claimed in Claim l, wherein the nonprostanoid prostaglandin I_2 agonist is

(1) [3-[[(1S)-2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-l-yl]methyl]phenoxy]acetic acid,

(2) [3-[[(1S)-2-(4,5-diphenyloxazol-2-yl)-2-cyclopenten-l-yl]methyl]phenoxy]acetic acid,

(3) [(2R)-5-(carboxymethoxy)-2-hydroxy-1,2,3,4-tetrahydronaphth-2-yl]methyl]N,N-diphenylcarbamate,

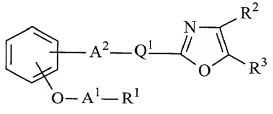
(4) (1R)-1-[(2R)-2-(4,5-diphenyloxazol-2-yl)pyrrolidin-l-yl]-5-carboxymethoxy-1,2,3,4-tetrahydronaphthalene or

(5) [3-[[(2R)-2-(4,5-diphenyloxazol-2-yl)pyrrolidin-l-yl]methyl]phenoxy]acetic acid,

or a pharmaceutically acceptable salt thereof.

Please add the following new Claims 9-12:

9. (New) A pharmaceutical composition as claimed in Claim 2, wherein the nonprostanoid prostaglandin I_2 agonist is a compound of the following general formula (I) or a pharmaceutically acceptable salt thereof:



(I)

[wherein R^1 is carboxy or protected carboxy,

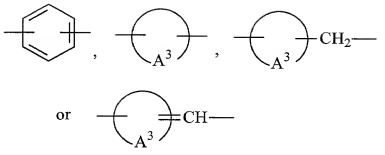
R^2 is aryl which may optionally have one or more suitable substituents,

R^3 is aryl which may optionally have one or more suitable substituents,

A^1 is lower alkylene,

A^2 is a single bond or lower alkylene and

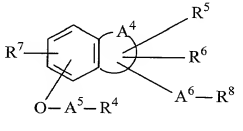
$-Q^1-$ is



(in which

represents cyclo(lower)alkane or cyclo(lower)alkene, which respectively may optionally have one or more suitable substituents)].

10. (New) A pharmaceutical composition as claimed in Claim 2, wherein the nonprostanoid prostaglandin I_2 agonist is a compound of the following general formula (II) or a pharmaceutically acceptable salt thereof:



(II)

[wherein R^4 is carboxy or protected carboxy,

R^5 is hydrogen, hydroxy or protected hydroxy,

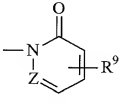
R^6 is hydrogen, hydroxy, protected hydroxy, lower alkyl or halogen,

R^7 is hydrogen or halogen,

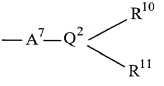
A^5 is lower alkylene,

A^6 is a single bond or lower alkylene and

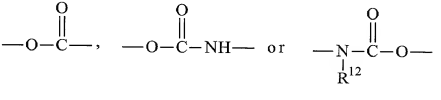
$-R^8$ is



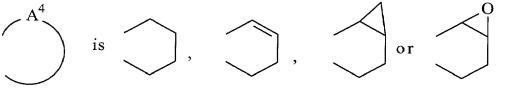
(in which R^9 is mono(or di or tri)aryl(lower)alkyl and Z is N or CH) or



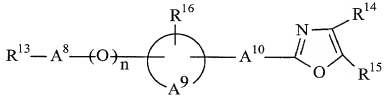
(in which $-A^7-$ is



(in which R^{12} is hydrogen or lower alkyl), Q^2 is N or CH, R^{10} is aryl and R^{11} is aryl), and



11. (New) A pharmaceutical composition as claimed in Claim 2, wherein the nonprostanoid prostaglandin I_2 agonist is a compound of the following general formula (III) or a pharmaceutically acceptable salt thereof



(III)

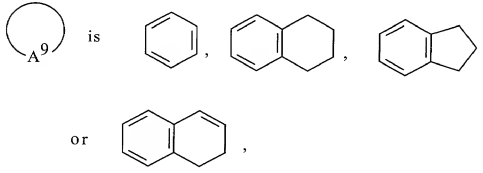
[wherein R^{13} is carboxy or protected carboxy,

R^{14} is aryl which may optionally have one or more suitable substituents,

R^{15} is aryl which may optionally have one or more suitable substituents,

R^{16} is hydrogen, lower alkyl, hydroxy or aryl,

A^8 is lower alkylene,



is

or

,

$-A^{10}-$ is

(in which $-A^{11}-$ is a single bond, $-CH_2-$ or -CO-,

represents cyclo(C5-C8)alkene, cyclo(C7-C8)alkane, bicycloheptane, bicycloheptene, tetrahydrofuran, tetrahydrothiophene, azetidine, pyrrolidine or piperidine, which respectively may optionally have one or more suitable substituents) or -X-A^{13}- (in which –X– is –O–, –S–, or –N(R^{17})- (R^{17} being hydrogen, lower alkyl or acyl) and A^{13} is lower alkylene which may optionally have one or more suitable substituents) and n is 0 or 1].

12. (New) A pharmaceutical composition as claimed in Claim 2, wherein the nonprostanoid prostaglandin I_2 agonist is

(1) [3-[[(1S)-2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl]phenoxy]acetic acid,

(2) [3-[[(1S)-2-(4,5-diphenyloxazol-2-yl)-2-cyclopenten-1-yl]methyl]phenoxy]acetic acid,

(3) [(2R)-5-(carboxymethoxy)-2-hydroxy-1,2,3,4-tetrahydronaphth-2-yl]methyl]N,N-diphenylcarbamate,

(4) (1R)-1-[(2R)-2-(4,5-diphenyloxazol-2-yl)pyrrolidin-1-yl]-5-carboxymethoxy-1,2,3,4-tetrahydronaphthalene or

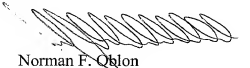
(5) [3-[[(2R)-2-(4,5-diphenyloxazol-2-yl)pyrrolidin-1-yl]methyl]phenoxy]acetic acid, or a pharmaceutically acceptable salt thereof.

REMARKS

Claims 1-12 are active in the present application. Claims 3-6 have been amended to remove multiple dependency. Claims 9-12 are new claims. Support for the new claims is found in the original claims. No new matter is added. An action on the merits and allowance of claims is solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



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Attorney of Record
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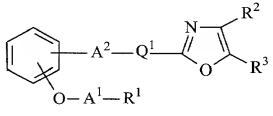
Marked-Up Copy
Serial No:

Amendment Filed on:
12-21-01

IN THE CLAIMS

--3. (Amended) A pharmaceutical composition as claimed in Claim 1 [or 2], wherein the nonprostanoid prostaglandin I_2 agonist is a compound of the following general formula (I) or a pharmaceutically acceptable salt thereof:



(I)

[wherein R^1 is carboxy or protected carboxy,

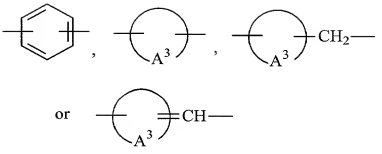
R^2 is aryl which may optionally have one or more suitable substituents,

R^3 is aryl which may optionally have one or more suitable substituents,

A^1 is lower alkylene,

A^2 is a single bond or lower alkylene and

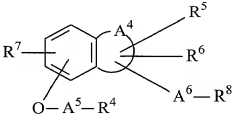
$-Q^1-$ is



(in which

represents cyclo(lower)alkane or cyclo(lower)alkene, which respectively may optionally have one or more suitable substituents)].

4. (Amended) A pharmaceutical composition as claimed in Claim 1 [or 2], wherein the nonprostanoid prostaglandin I_2 agonist is a compound of the following general formula (II) or a pharmaceutically acceptable salt thereof:



(II)

[wherein R^4 is carboxy or protected carboxy,

R^5 is hydrogen, hydroxy or protected hydroxy,

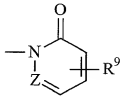
R^6 is hydrogen, hydroxy, protected hydroxy, lower alkyl or halogen,

R^7 is hydrogen or halogen,

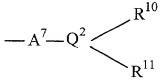
A^5 is lower alkylene,

A^6 is a single bond or lower alkylene and

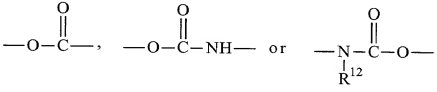
$-R^8$ is



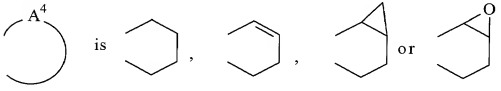
(in which R^9 is mono(or di or tri)aryl(lower)alkyl and Z is N or CH) or



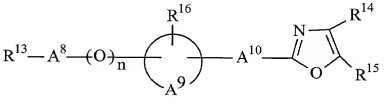
(in which $-A^7-$ is



(in which R^{12} is hydrogen or lower alkyl), Q^2 is N or CH, R^{10} is aryl and R^{11} is aryl), and



5. (Amended) A pharmaceutical composition as claimed in Claim 1 [or 2], wherein the nonprostanoid prostaglandin I_2 agonist is a compound of the following general formula (III) or a pharmaceutically acceptable salt thereof



(III)

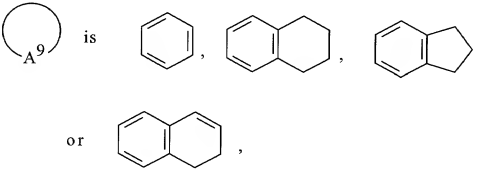
[wherein R^{13} is carboxy or protected carboxy,

R^{14} is aryl which may optionally have one or more suitable substituents,

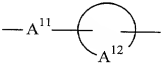
R^{15} is aryl which may optionally have one or more suitable substituents,

R^{16} is hydrogen, lower alkyl, hydroxy or aryl,

A^8 is lower alkylene,



$-A^{10}-$ is



(in which -A^{11}- is a single bond, -CH_2- or -CO-,

represents cyclo(C5-C8)alkene, cyclo(C7-C8)alkane, bicycloheptane, bicycloheptene, tetrahydrofuran, tetrahydrothiophene, azetidine, pyrrolidine or piperidine, which respectively may optionally have one or more suitable substituents) or -X-A^{13}- (in which –X– is –O–, –S–, or –N(R^{17})- (R^{17} being hydrogen, lower alkyl or acyl) and A^{13} is lower alkylene which may optionally have one or more suitable substituents) and n is 0 or 1].

6. (Amended) A pharmaceutical composition as claimed in Claim 1 [or 2], wherein the nonprostanoid prostaglandin I_2 agonist is

(1) [3-[[(1S)-2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-l-yl]methyl]phenoxy]acetic acid,

(2) [3-[[(1S)-2-(4,5-diphenyloxazol-2-yl)-2-cyclopenten-l-yl]methyl]phenoxy]acetic acid,

(3) [(2R)-5-(carboxymethoxy)-2-hydroxy-1,2,3,4-tetrahydronaphth-2-yl]methyl]N,N-diphenylcarbamate,

(4) (1R)-1-[(2R)-2-(4,5-diphenyloxazol-2-yl)pyrrolidin-l-yl]-5-carboxymethoxy-1,2,3,4-tetrahydronaphthalene or

(5) [3-[[(2R)-2-(4,5-diphenyloxazol-2-yl)pyrrolidin-l-yl]methyl]phenoxy]acetic acid, or a pharmaceutically acceptable salt thereof.

Claims 9-12 (New).--

DESCRIPTION

REMEDIES FOR SKIN ULCER

TECHNICAL FIELD

The present invention relates to a pharmaceutical composition comprising a nonprostanoid prostaglandin I_2 agonist as an active ingredient.

The present invention relates to a novel use of a nonprostanoid prostaglandin I_2 agonist.

More particularly, it is an object of the present invention to provide a pharmaceutical composition which comprises a nonprostanoid prostaglandin I_2 agonist as an active ingredient and is intended for use in the prevention and/or treatment of skin ulcer [e.g. diabetic skin ulcer, inclusive of ulcer of lower limb, burn ulcer (burn), traumatic ulcer, crural (cnemial) ulcer, diabetic gangrene, etc.] and decubitus ulcer (bedsore) and the like, particularly diabetic skin ulcer, in humans or animals.

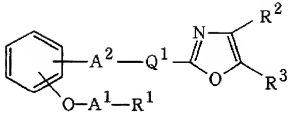
DISCLOSURE OF INVENTION

The inventors of this invention found that nonprostanoid prostaglandin I_2 agonists are useful in the prevention and/or treatment of skin ulcer [e.g. diabetic skin ulcer, inclusive of ulcer of lower limb, burn ulcer (burn), traumatic ulcer, crural (cnemial) ulcer, diabetic gangrene, etc.] and decubitus ulcer (bedsore), particularly diabetic skin ulcer, in humans or animals and, based on this finding, they have now completed the present invention.

The present invention is practiced by preparing a pharmaceutical composition comprising a nonprostanoid prostaglandin I_2 agonist as an active ingredient and administering the same to humans or animals for the prevention and/or treatment of skin ulcer [e.g. diabetic skin ulcer, inclusive of ulcer of lower limb, burn ulcer (burn), traumatic ulcer, crural (cnemial) ulcer, diabetic gangrene, etc.] and decubitus ulcer (bedsore), particularly diabetic skin ulcer.

The nonprostanoid prostaglandin I_2 agonist to be used in accordance with this invention is a prostaglandin I_2 agonist having no prostaglandin skeleton or bicylco[3.3.0]octane skeleton or 2-oxabicyclo[3.3.0]octane skeleton.

Preferred as the nonprostanoid prostaglandin I_2 agonist in the practice of the invention are the following compounds (I):



(I)

[wherein R^1 is carboxy or protected carboxy,

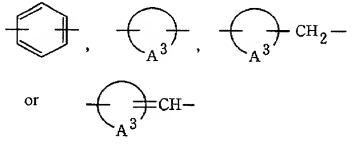
R^2 is aryl which may optionally have one or more suitable substituents,

R^3 is aryl which may optionally have one or more suitable substituents,

A^1 is lower alkylene,

A^2 is a single bond or lower alkylene and

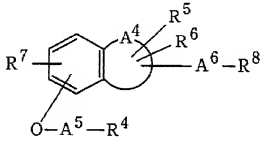
$-Q^1-$ is



(in which

represents cyclo(lower)alkane or cyclo(lower)alkene, which respectively may optionally have one or more suitable substituents)];

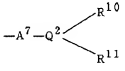
or the following compounds (II):



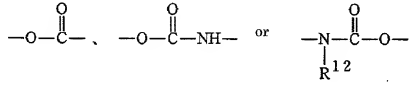
(II)

[wherein R^4 is carboxy or protected carboxy,
R^5 is hydrogen, hydroxy or protected hydroxy,
R^6 is hydrogen, hydroxy, protected hydroxy, lower alkyl or halogen,
R^7 is hydrogen or halogen,
A^5 is lower alkylene,
A^6 is a single bond or lower alkylene and
$-R^8$ is

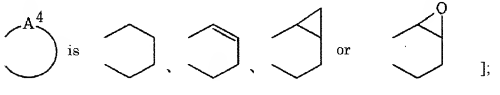
(in which R^9 is mono(or di or tri)aryl(lower)alkyl and Z is N or CH) or



(in which A^7 is

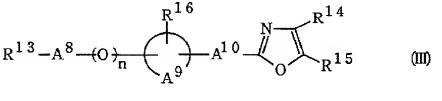


(in which R^{12} is hydrogen or lower alkyl), Q^2 is N or CH, R^{10} is aryl and R^{11} is aryl), and



];

or the following compounds (III):

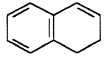


(III)

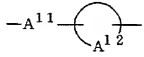
[wherein R^{13} is carboxy or protected carboxy,
R^{14} is aryl which may optionally have one or more suitable substituents,
R^{15} is aryl which may optionally have one or more suitable substituents,
R^{16} is hydrogen, lower alkyl, hydroxy or aryl,
A^8 is lower alkylene,

is

or



$-A^{10}-$ is



(in which $-A^{11}-$ is a single bond, $-CH_2-$ or –CO-,

represents cyclo(C5-C8)alkene, cyclo(C7-C8)alkane, bicycloheptane, bicycloheptene, tetrahydrofuran, tetrahydrothiophene, azetidine, pyrrolidine or piperidine, which respectively may optionally have one or more suitable substituents) or
$-X-A^{13}-$ (in which –X- is –O-, -S-, or $-N(R^{17})-$ (R^{17} being hydrogen, lower alkyl or acyl) and A^{13} is lower alkylene which may optionally have one or more suitable substituents) and
n is 0 or 1];
or pharmaceutically acceptable salts thereof.

Suitable salts for use as the pharmaceutically acceptable salts of compounds (I) to (III) are conventional nontoxic salts, including alkali metal salts (e.g. sodium salt, potassium salt, etc.), alkaline earth metal salts (e.g. calcium salt, magnesium salt, etc.), ammonium salt, organic base salts (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), organic acid salts (e.g. acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, etc.), inorganic acid salts (e.g. hydrochloride, hydrobromide, sulfate, phos-

phate, etc.), salts with amino acids (e.g. arginine, aspartic acid, glutamic acid, etc.) and the like.

The compounds (I) to (III) and pharmaceutically acceptable salts thereof, which are to be used in accordance with this invention, may contain one or more asymmetric centers and therefore they may exist as enantiomers or diastereoisomers. Both mixtures of such isomers and individual isomers fall within the scope of this invention.

The compounds (I) to (III) and pharmaceutically acceptable salts thereof, which are to be used in accordance with this invention, may exist a solvate and this solvate also falls within the scope of this invention. As preferred solvate, there may be mentioned hydrates, ethanolates and the like.

Radiolabeled derivatives of the compounds (I) to (III), which are suited for use in biological studies, also fall within the scope of this invention.

Referring to the above description and subsequent description in the present specification, suitable examples and specific examples falling within respective definitions given herein for defining the scope of the present invention are shown below in detail.

Unless otherwise specified, the term "lower" means that 1 to 6 carbon atoms are involved.

Suitable species of "aryl" and of "aryl moiety" of "mono(or di or tri)aryl(lower)alkyl" are phenyl, naphthyl and the like.

Preferred as "lower alkylene" are straight or branched ones containing 1 to 6 carbon atoms, such as methylene, ethylene, trimethylene, tetramethylene, pentamethylene and hexamethylene. More preferred are those containing 1 to 3 carbon atoms.

Preferred as "lower alkyl" or as "lower alkyl moiety" of "mono(or di or tri)aryl(lower)alkyl" are straight or branched ones containing 1 to 6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl and hexyl. More preferred are those containing 1 to 4 carbon atoms.

Preferred as "protected carboxy" are esterified carboxy etc.

Preferred examples of the ester moiety of the esterified carboxy are (1) lower alkyl esters (e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, tert-butyl ester, pentyl ester, hexyl ester, etc.), which may optionally have at least one suitable substituent, thus including, for example, lower alkanoyloxy(lower)alkyl esters [e.g. acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 1-(or 2-)acetoxyethyl ester, 1-(or 2- or 3-)acetoxypropyl ester, 1-(2-, 3- or 4-)acetoxybutyl ester, 1-(or 2-)propionyloxyethyl ester, 1-(or 2- or 3-)propionyloxypropyl ester, 1-(or 2-)butyryloxyethyl ester, 1-(or 2-)isobutyryloxyethyl ester, 1-(or 2-)pivaloyloxyethyl ester, 1-(or 2-)hexanoyloxyethyl ester,

isobutyryloxymethyl ester, 2-ethylbutyryloxymethyl ester, 3,3-dimethylbutyryloxymethyl ester, 1-(or 2-)pentanoyloxyethyl ester, etc.], lower alkylsulfonyloxy(lower)alkyl esters (e.g. 2-mesylethyl ester etc.), mono(or di- or tri-)halo(lower)alkyl esters (e.g. 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.), lower alkoxycarbonyloxy(lower)alkyl esters (e.g. methoxycarbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, 2-methoxycarbonyloxyethyl ester, 1-ethoxycarbonyloxyethyl ester, 1-isopropoxycarbonyloxyethyl ester, etc.), phthalidylidene(lower)alkyl esters, (5-(lower)alkyl-2-oxo-1,3-dioxol-4-yl)(lower)alkyl esters [e.g. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl ester, etc.];

(2) lower alkenyl esters (e.g. vinyl ester, allyl ester, etc.);

(3) lower alkynyl esters (e.g. ethynyl ester, propynyl ester, etc.);

(4) ar(lower)alkyl esters, which may optionally have at least one suitable substituent, for example mono(or di- or tri-)phenyl(lower)alkyl esters, which may optionally have at least one suitable substituent, (e.g. benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-tert-butylbenzyl ester, etc.);

(5) aryl esters which may optionally have at least one suitable substituent (e.g. phenyl ester, 4-chlorophenyl ester, tolyl ester, tert-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, etc.);

(6) phthalidyl ester, and so forth.

Referring to the expression "aryl which may optionally have at least one suitable substituent", halogen, amino, hydroxy, lower alkoxy and such lower alkyl species as mentioned above are preferred as "substituent".

Suitable examples of "cyclo(lower)alkane" are cyclopropane, cyclobutane, cyclopentane and cyclohexane.

Suitable examples of "cyclo(lower)alkene" are cyclopropene, cyclobutene, cyclopentene and cyclohexene.

Referring to the expression "cyclo(lower)alkane or cyclo(lower)alkene, which respectively may optionally have one or more suitable substituents", epoxy, hydroxy, lower alkoxy and the like are preferred as "substituents".

Suitable examples of "lower alkoxy" are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, tert-pentyloxy, hexyloxy and the like.

Preferred as "protected hydroxy" are acyloxy etc.

Preferred as "acyl" and as "acyl moiety" of "acyloxy" are aliphatic acyl groups and acyl groups having an aromatic or heterocyclic ring.

As preferred examples of the acyl, there may be mentioned lower alkanoyl groups

(e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, oxalyl, succinyl, pivaloyl, etc.);

lower alkoxycarbonyl groups (e.g. methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert-butoxycarboyl, pentyloxycarbonyl, hexyloxycarbonyl, etc.):

lower alkylsulfonyl groups (e.g. mesyl, ethanesulfony, propanesulfonyl, ispropanesulfonyl, butanesuflonyl, etc.);

arenesulfonyl groups (e.g. benzenesulfonyl, tosyl, etc.);

aroyl groups (e.g. benzoyl, toluoyl, xyloyl, naphthoyl, phthaloyl, indanecarbonyl, etc.);

ar(lower)alkanoyl groups (e.g. phenylacetyl, phenylpropionyl, etc.);

ar(lower)alkoxycarbonyl groups (e.g. benzyloxycarbonyl, phenethyloxycarbonyl, etc.); and so on.

Suitable examples of "halogen" are chlorine, bromine, iodine and fluorine.

Preferred species of "cyclo(C5-C8)alkene" are cyclopentene, cyclohexene, cyclopentene and cyclooctene.

Preferred species of "cyclo(C7-C8)alkane" are cycloheptane and cyclooctane.

Preferred as "bicyclcoheptane" are bicyclo[2.2.1]heptane etc.

Preferred as "bicycloheptene" are bicyclo[2.2.1]heptene such as bicyclo[2.2.1]hept-2-ene, and the like.

Referring to the expression "cyclo(C5-C8)alkene, cyclo(C7-C8)alkane, bicycloheptane, bicycloheptene, tetrahydrofuran, tetrahydrothiophene, azetidine, pyrrolidine or piperidine, which respectively may optionally have one or more suitable substituents", imino, hydroxy, oxo, such acyl species as mentioned above, imino-protecting groups and the like are preferred as "substituents".

Suitable "imino-protecting groups" are mono(or di or tri)aryl(lower)alkyl groups and the like.

Referring to the expression "lower alkylene which may optionally have one or more suitable substituents", suitable "substituents" include such lower alkyl species as mentioned above, hydroxy lower alkyl (e.g. hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, etc.) and the like.

Preferred embodiments of compounds (I) are as follows:

Those in which R^1 is carboxy, or protected carboxy (more preferably esterified carboxy, most preferably lower alkoxycarbonyl),

R^2 is aryl, which may optionally have one to three (more preferably one) suitable substituents (more preferably phenyl or lower alkylphenyl),

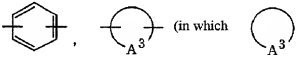
R^3 is aryl which may optionally have one to three (more preferably one) suitable substitu-

ents (more preferably phenyl or lower alkylphenyl),

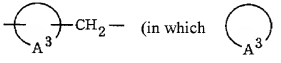
A^1 is lower alkylene (more preferably C1-C3 alkylene, most preferably methylene),

A^2 is a single bond, or lower alkylene (more preferably C1-C3 alkylene, most preferably methylene), and

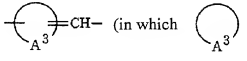
Q^1- is



is cyclo(lower)alkane which may optionally have one substituent selected from the group consisting of epoxy, hydroxy and lower alkoxy, or cyclo(lower)alkene) or



is cyclo(lower)alkane which may optionally have one substituent selected from the group consisting of epoxy and hydroxy, or cyclo(lower)alkene) or



is cyclo(lower)alkane.

Preferred embodiments of compounds (II) are as follows:

Those in which R^4 is carboxy, or protected carboxy (more preferably esterified carboxy, most preferably lower alkoxycarbonyl),

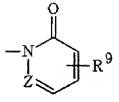
R^5 is hydrogen, hydroxy, or protected hydroxy (more preferably acyloxy),

R^6 is hydrogen, hydroxy, protected hydroxy (more preferably acyloxy), lower alkyl or halogen,

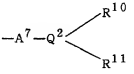
A^5 is lower alkylene (more preferably C1-C3 alkylene, most preferably methylene),

A^6 is a single bond, or lower alkylene (more preferably C1-C3 alkylene, most preferably methylene or ethylene),

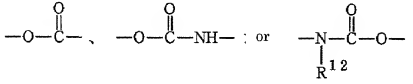
$-R^8$ is



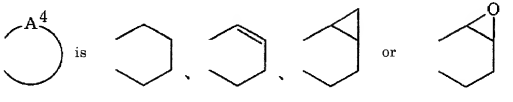
(in which R^9 is diaryl(lower)alkyl (more preferably diphenyl(lower)alkyl, most preferably diphenylmethyl) and Z is N or CH) or



(in which $-A^7-$ is



(R^{12} being hydrogen or lower alkyl),
Q^2 is N or CH,
R^{10} is aryl (more preferably phenyl),
R^{11} is aryl (more preferably phenyl) and

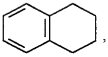


Preferred embodiments of compounds (III) are as follows:
Those in which R^{13} is carboxy, or protected carboxy (more preferably esterified carboxy, most preferably lower alkoxycarbonyl),
R^{14} is aryl which may optionally have lower alkyl (more preferably phenyl or lower alkylphenyl, most preferably phenyl or C1-C4 alkylphenyl),
R^{15} is aryl which may optionally have lower alkyl (more preferably phenyl or lower alkylphenyl, most preferably phenyl or C1-C4 alkylphenyl),
R^{16} is hydrogen, lower alkyl (more preferably C1-C4 alkyl, most preferably methyl), hydroxy or aryl (more preferably phenyl),
A^8 is lower alkylene (more preferably C1-C4 alkylene, most preferably methylene or ethyl-

ene),

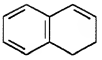
is

,



,

or

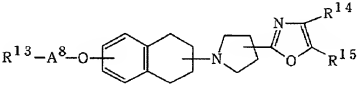


$-A^{10}-$ is

(in which $-A^{11}-$ is a single bond, $-CH_2-$ or –CO-,

is cyclo(C5-C8)alkene, cyclo(C7-C8)alkane, bicycloheptane (more preferably bicyclo[2.2.1]heptane), bicycloheptene (more preferably bicyclo[2.2.1]heptene, most preferably bicyclo[2.2.1]hept-2-ene), tetrahydrofuran, tetrahydrothiophene, azetidine, pyrrolidine or piperidine, which respectively may optionally have one to three (more preferably one or two) substituents each selected from the group consisting of imino, oxo, acyl (more preferably lower alkanoyl, most preferably C1-C4 alkanoyl) and imino protecting groups (more preferably mono(di or tri)phenyl(lower)alkyl, most preferably phenyl(lower)alkyl) or $-X-A^{13}-$ (in which –X- is –O-, -S-, or $-N(R^{17})-$ (R^{17} being hydrogen, lower alkyl(more preferably C1-C4 alkyl) or acyl (more preferably lower alkanoyl, most preferably C1-C4 alkanoyl)) and A^{13} is lower alkylene (more preferably C1-C4 alkylene, most preferably methylene or ethylene) which may optionally have one to three (more preferably one) suitable substituents selected from the group consisting of lower alkyl (more preferably C1-C4 alkyl) and hydroxy(lower)alkyl (more preferably hydroxy(C1-C4)alkyl)) and
n is 0 or 1.

More preferred among compounds (III) are compounds of the following formula (III-A):



(III–A)

wherein R^{13} is carboxy, or protected carboxy (more preferably esterified carboxy, most

preferably lower alkoxycarboyl),

R^{14} is phenyl, or lower alkylphenyl (more preferably C1-C4 alkylphenyl),

R^{15} is phenyl, or lower alkylphenyl (more preferably C1-C4 alkylphenyl),

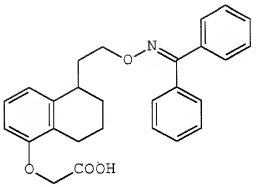
A^8 is lower alkylene (more preferably C1-C4 alkylene, most preferably methylene).

Particularly preferred nonprostanoid prostaglandin I_2 agonists to be used in the practice of the present invention are [3-[[(1S)-2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl]phenoxy]acetic acid, [3-[[(1S)-2-(4,5-diphenyoxazol-2-yl)-2-cyclopenten-1-yl]methyl] phenoxy]acetic acid,
[[(2R)-5-(carboxymethoxy)-2-hydroxy-1,2,3,4-tetrahydronaphth-2-yl]methyl] N,N-diphenylcarbamate,
(1R)-1-[(2R)-2-(4,5-diphenyloxazol-2-yl)pyrrolidin-1-yl]-5-carboxymethoxy-1,2,3,4-tetrahydronaphthalene, [3-[[(2R)-2-(4,5-diphenyloxazol-2-yl)pyrrolidin-1-yl]methyl]phenoxy]acetic acid and salts of these.

The compounds of general formulas (I), (II) and (III) as well as the specific compounds mentioned above are novel or known compounds and can be prepared by the methods described in the publications cited below or methods analogous thereto (those publications cited herein are incorporated by reference):
International publication number: WO 95/17393;
International publication number: WO 95/24393;
International publication number: WO 97/03973.

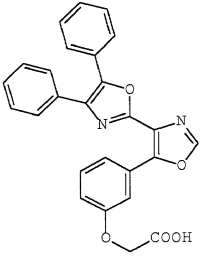
As other preferred examples of the nonprostanoid prostaglandin I_2 agonist which are to be used in the practice of the present invention, there may be mentioned the following:

(1) Condensed benzene-oxyacetic acid derivatives described in European publication Nos. EP 578847 A, EP 548949 A, EP 542203 A1, EP 581187 A or EP 558062·A (those publications cited herein are incorporated by reference), preferably the compound of the following formula (IV) or salts thereof:



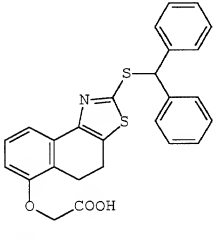
(IV)

(2) Phenoxyacetic acid derivatives described in U.S. Patent 348969 (this publication cited herein is incorporated by reference), preferably the compound of the following formula (V) or salts thereof:



(V)

(3) Tricyclic compounds described in International laid-open number WO 98/13356 (this publication cited herein is incorporated by reference), preferably the compound of the following formula (VI) or salts thereof:



(VI)

and the like.

The pharmaceutical composition for use in the prevention and/or treatment of skin ulcer according to the present invention can be used in the form of pharmaceutical preparations containing a nonprostanoid prostaglandin I_2 agonist as an active ingredient, for example solids, semisolids or liquids (e.g. tablets, pellets, troches, capsules, suppositories, creams, ointments, aerosols, powders, solutions, emulsions, suspensions, etc.) suited for rectal, pulmonary (nasal or oral inhalation), transnasal, intraocular, external (local), oral or parenteral (including hypodermic, intravenous and intramuscular) routes of administration or for inhalation.

The pharmaceutical composition of this invention may contain one or more of various organic or inorganic carrier substances commonly used for pharmaceutical purposes, for example excipients (e.g. sucrose, starch, mannitol, sorbitol, lactose, glucose, cellulose, talc, calcium phosphate, calcium carbonate, etc.), binding agents (e.g. cellulose, methylcellulose, hydroxypropylcellulose, polypropylpyrrolidone, gelatin, gum arabic, polyethylene glycol, sucrose, starch, etc.), disintegrants (e.g. starch, carboxymethylcellulose, carboxymethylcellulose calcium, hydroxypropylstarch, sodium starchglycolate, sodium hydrogen carbonate, calcium phosphate, calcium citrate, etc.), lubricants (e.g. magnesium stearate, talc, sodium lauryl sulfate, etc.), flavorings or corrigents (e.g. citric acid, menthol, glycine, orange peel powder, etc.), preservatives (e.g. sodium benzoate, sodium hydrogen sulfite, methylparaben, propylparaben, etc.), stabilizers (e.g. citric acid, sodium citrate, acetic acid, etc.), suspending agents (e.g. methylcellulose, polyvinylpyrrolidone, aluminum stearate, etc.), dispersing agents, aqueous diluents (e.g. water) and base waxes (e.g. cacao butter, polyethylene glycol, white petrolatum, etc.).

Generally, the active ingredient may be administered in a unit dose of 0.01 mg/kg to 50 mg/kg once to four times a day. However, the dosage may be increased or decreased according to the age, body weight and condition of the patient or the route of administration.

In cases where it is administered in the form of a lotion, gel or cream, the active substance may be locally administered at a concentration of 0.0001 to 10% (preferably 0.01 to 5%) several times daily, for example twice to five times daily.

BEST MODES FOR CARRYING OUT THE INVENTION

The test compound used as a representative example of the nonprostanoid prostaglandin I_2 agonist in the practice of the present invention, namely [[(2R)-5-(carboxymethoxy)-2-hydroxy-1,2,3,4-tetrahydro-2-naphthyl]methyl] N,N-diphenylcarbamate, can be synthesized by the method described in International publication number WO 95/24393 or a method analogous thereto.

EFFECT OF THE INVENTION

To demonstrate the usefulness of the nonprostanoid prostaglandin I_2 agonist used in the invention for the prevention or treatment of skin ulcer in human or animals, pharmacology test data on a representative compound, namely (1) [[(2R)-5-(carboxymethoxy)-2-hydroxy-1,2,3,4-tetrahydronaphth-2-yl]methyl] N,N-diphenylcarbamate (hereinafter referred to as test compound), are presented below.

Test Example 1 (db/db mouse full-thickness wound model)

[Experimental]

Using 10-week-old male C57BL/KsJ db/db mice (db/db mice) and the corresponding control C57BL/KsJ +m/+m mice (+m/+m mice), the back hair coat was removed with a depilatory cream. After 3 days, using ophthalmological scissors, the skin in a circular area with a diameter of about 1.5 cm at the dorsal midline was removed to construct a full-thickness wound. Thereafter, the full-thickness wound area was covered with a polyurethane film agent. During 18 consecutive days beginning the day of wound construction, 100 µl of the investigational compound solution or distilled water (vehicle) was taken in a syringe and applied through the polyurethane film once daily. The polyurethane film agent was changed every day and after disinfection with 3% H_2O_2, the drug was applied in the same manner as above. The wound area was measured by the tracing method under light anesthesia every other day as a rule. With the initial wound area at the beginning of drug application being taken as 100%, the fractional area at each day of measurement was calculated.

[Results]

The wound area in db/db mice expanded slightly in an early stage following construction of the wound and thereafter diminished day by day. Compared with the wound area in +m/+m mice, the area was significantly larger at every measurement day, indicating a delay in healing. In contrast, in the groups treated with 0.01% and 0.1% solutions of the investigational drug, the early expansion of wound area was not observed and the wound area diminished day by day and a significant difference ($p<0.05$) from the vehicle control group was observed in wound area on and after day 7 and day 4, respectively, following construction of the wound. Comparison in the wound area on the last observation day (day 18 following wound construction) showed that whereas the area reduction in the vehicle treatment group was 73%, the reductions in the groups treated with 0.01% and 0.1% solutions of the investigational compound were 90% and 93%, respectively. These results indicate that the investigational compound has a wound healing-promoting action.

INDUSTRIAL APPLICABILITY

The above-described nonprostanoid prostaglandin I_2 agonist of the invention is of

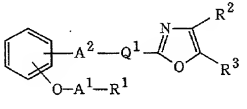
value in the prevention and/or treatment of skin ulcers (for example, diabetic skin ulcer inclusive of ulcer of lower limb, burn ulcer (burn), traumatic ulcer, crural (cnemial) ulcer, diabetic gangrene, etc.) and decubitus ulcer (bedsore), particularly diabetic skin ulcer, in humans or animals.

CLAIMS

1. A pharmaceutical composition for the prevention and/or treatment of skin ulcer or bedsore in humans or animals which comprises a nonprostanoid prostaglandin I_2 agonist as an active ingredient.

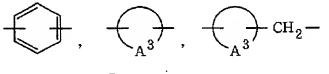
2. A pharmaceutical composition for the prevention and/or treatment of diabetic skin ulcer in humans or animals which comprises a nonprostanoid prostaglandin I_2 agonist as an active ingredient.

3. A pharmaceutical composition as claimed in Claim 1 or 2, wherein the nonprostanoid prostaglandin I_2 agonist is a compound of the following general formula (I) or a pharmaceutically acceptable salt thereof:

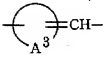


(I)

[wherein R^1 is carboxy or protected carboxy,
R^2 is aryl which may optionally have one or more suitable substituents,
R^3 is aryl which may optionally have one or more suitable substituents,
A^1 is lower alkylene,
A^2 is a single bond or lower alkylene and
$-Q^1-$ is



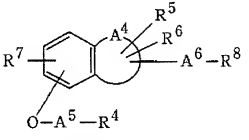
or



(in which

represents cyclo(lower)alkane or cyclo(lower)alkene, which respectively may optionally have one or more suitable substituents)].

4. A pharmaceutical composition as claimed in Claim 1 or 2, wherein the nonprostanoid prostaglandin I_2 agonist is a compound of the following general formula (II) or a pharmaceutically acceptable salt thereof:



(II)

[wherein R" is carboxy or protected carboxy,

R^5 is hydrogen, hydroxy or protected hydroxy,

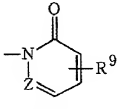
R^6 is hydrogen, hydroxy, protected hydroxy, lower alkyl or halogen,

R^7 is hydrogen or halogen,

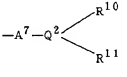
A^5 is lower alkylene,

A^6 is a single bond or lower alkylene and

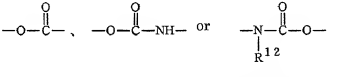
$-R^8$ is



(in which R^9 is mono(or di or tri)aryl(lower)alkyl and Z is N or CH) or

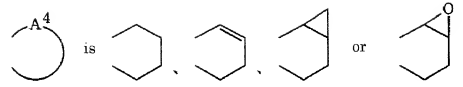


(in which $-A^7-$ is

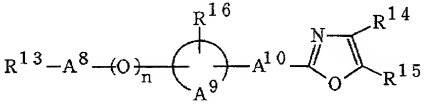


or

(in which R^{12} is hydrogen or lower alkyl), Q^2 is N or CH, R^{10} is aryl and R^{11} is aryl), and

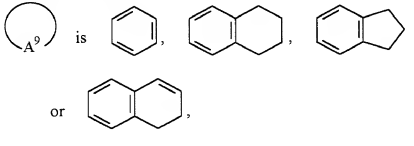


5. A pharmaceutical composition as claimed in Claim 1 or 2, wherein the nonprostanoid prostaglandin I_2 agonist is a compound of the following general formula (III) or a pharmaceutically acceptable salt thereof:

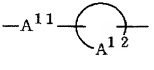


(III)

[wherein R^{13} is carboxy or protected carboxy,
R^{14} is aryl which may optionally have one or more suitable substituents,
R^{15} is aryl which may optionally have one or more suitable substituents,
R^{16} is hydrogen, lower alkyl, hydroxy or aryl,
A^8 is lower alkylene,



-A^{10}- is



(in which -A^{11}- is a single bond, -CH_2– or –CO-,

represents cyclo(C5-C8)alkene, cyclo(C7-C8)alkane, bicycloheptane, bicycloheptene, tetrahydrofuran, tetrahydrothiophene, azetidine, pyrrolidine or piperidine, which respectively may optionally have one or more suitable substituents) or

-X-A^{13}- (in which –X- is –O-, -S-, or –N(R^{17})- (R^{17} being hydrogen, lower alkyl or acyl) and A^{13} is lower alkylene which may optionally have one or more suitable substituents) and n is 0 or 1].

6. A pharmaceutical composition as claimed in Claim 1 or 2, wherein the nonprostanoid prostaglandin I_2 agonist is

(1) [3-[[(1S)-2-(4,5-diphenyloxazol-2-yl)-2-cyclohexen-1-yl]methyl]phenoxy]acetic acid,

(2) [3-[[(1S)-2-(4,5-diphenyloxazol-2-yl)-2-cyclopenten-1-yl]methyl]phenoxy]acetic acid,

(3) [(2R)-5-(carboxymethoxy)-2-hydroxy-1,2,3,4-tetrahydronaphth-2-yl]methyl] N,N-diphenylcarbamate,

(4) (1R)-1-[(2R)-2-(4,5-diphenyloxazol-2-yl)pyrrolidin-1-yl]-5-carboxymethoxy-1,2,3,4-tetrahydronaphthalene or

(5) [3-[[(2R)-2-(4,5-diphenyloxazol-2-yl)pyrrolidin-1-yl]methyl]phenoxy]acetic acid,

or a pharmaceutically acceptable salt thereof.

7. The use of a nonprostanoid prostaglandin I_2 agonist in the manufacture of pharmaceutical compositions for use in the prevention and/or treatment of skin ulcer or bedsore in humans or animals.

8. A method for the prevention and/or treatment of skin ulcer or bedsore which comprises administering an effective amount of a nonprostanoid prostaglandin I_2 agonist to a human or animal requiring such prevention and/or treatment.

Declaration, Power Of Attorney and Petition

WE (I) the undersigned inventor(s), hereby declare(s) that:

My residence, post office address and citizenship are as stated below next to my name,

We (I) believe that we are (I am) the original, first, and joint (sole) inventor(s) of the subject matter which is claimed and for which a patent is sought on the invention entitled

REMEDIES FOR SKIN ULCER

the specification of which

☐ is attached hereto.

☐ was filed on _____ as
Application Serial No. _____
and amended on _____.

☐ was filed as PCT international application
Number PCT/JP00/03935
on June 16, 2000,
and was amended under PCT Article 19
on _____ (if applicable).

We (I) hereby state that we (I) have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

We (I) acknowledge the duty to disclose information known to be material to the patentability of this application as defined in Section 1.56 of Title 37 Code of Federal Regulations.

We (I) hereby claim foreign priority benefits under 35 U.S.C. § 119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. Prior Foreign Application(s)

Application No.	Country	Day/Month/Year	Priority Claimed
11/173763	Japan	21/06/99	☒ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No
			☐ Yes ☐ No

We (I) hereby claim the benefit under Title 35, United States Code, § 119(e) of any United States provisional application(s) listed below.

(Application Number)	(Filing Date)
(Application Number)	(Filing Date)

We (I) hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

Application Serial No.	Filing Date	Status (pending, patented, abandoned)
PCT/JP00/03935	June 16, 2000	

And we (I) hereby appoint: Norman F. Oblon, Reg. No. 24,618; Marvin J. Spivak, Reg. No. 24,913; C. Irvin McClelland, Reg. No. 21,124; Gregory J. Maier, Reg. No. 25,599; Arthur I. Neustadt, Reg. No. 24,854; Richard D. Kelly, Reg. No. 27,757; James D. Hamilton, Reg. No. 28,421; Eckhard H. Kuesters, Reg. No. 28,870; Robert T. Pous, Reg. No. 29,099; Charles L. Gholz, Reg. No. 26,395; William E. Beaumont, Reg. No. 30,996; Jean-Paul Lavalleye, Reg. No. 31,451; Stephen G. Baxter, Reg. No. 32,884; Richard L. Treanor, Reg. No. 36,379; Steven P. Weihrouch, Reg. No. 32,829; John T. Goolkasian, Reg. No. 26,142; Richard L. Chinn, Reg. No. 34,305; Steven E. Lipman, Reg. No. 30,041; Carl E. Schlier, Reg. No. 34,426; James J. Kulbaski, Reg. No. 34,648; Richard A. Neifeld, Reg. No. 35,299; J. Derek Mason, Reg. No. 35,270; Surinder Sachar, Reg. No. 34,423; Jeffrey B. McIntyre, Reg. No. 36,867; William T. Enos, Reg. No. 33,128; Michael E. McCabe, Jr., Reg. No. 37,182; Bradley D. Lytle, Reg. No. 40,073; and Michael R. Casey, Reg. No. 40,294; our (my) attorneys, with full powers of substitution and revocation, to prosecute this application and to transact all business in the Patent Office connected therewith; and we (I) hereby request that all correspondence regarding this application be sent to the firm of OBLON, SPIVAK, McCLELLAND, MAIER & NEUSTADT, P.C., whose Post Office Address is: Fourth Floor, 1755 Jefferson Davis Highway, Arlington, Virginia 22202.

We (I) declare that all statements made herein of our (my) own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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NOV. 29. 2001
Date

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Signature of Inventor

Date

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NAME OF FOURTH JOINT INVENTOR

Signature of Inventor

Date

Residence:

Citizen of:

Post Office Address:

NAME OF FIFTH JOINT INVENTOR

Signature of Inventor

Date

Residence:

Citizen of:

Post Office Address: